DECLARATION UNDER 37 C.F.R. § 1.132 OF DR. JOSEPH M. PATTI, PH.D.		
	Application #	09/810,428
	Confirmation #	6490
	Filing Date	19 March 2001
	First Inventor	HOOK et al.
	Art Unit	1645
	Examiner	Baskar
	Docket #	P06668US03/BAS

I, Dr. Joseph M. Patti, Ph.D., declare and state as follows:

1. I am one of the inventors of the above-identified patent application, and I am currently the Vice President of Clinical Research for Inhibitex, a company that specializes in products and research regarding extracellular matrix proteins and monoclonal antibodies generated thereto including those embodied in the present invention. In addition to being a co-inventor of numerous US Patents in this general field, including most recently U.S. Pat. No. 6,288,214 for Collagen Binding Protein Compositions and Methods of Use, U.S. Pat. No. 6,680,195, for Extracellular matrix-binding proteins from *Staphylococcus aureus*, U.S. Pat. No. 6,685,943, Fibronectin binding protein compositions and methods of use, and U.S. Pat. No. 6,692,739, Staphylococcal immunotherapeutics via donor selection and donor stimulation, and I have also authored or co-authored numerous journal articles in this field. I am thus well familiar with the subject matter of the present invention.

2. The present invention relates in particular to an isolated monoclonal antibody which not only recognizes the CNA19 region from *S. aureus*, it is cross-reactive to *S. epidermidis* in a manner not possible prior to the present invention and is also capable of displacing *S. aureus* when bound to an extracellular matrix protein. As

Applicants have previously indicated, the cross-reactivity of the CNA19 antibody to *S. epidermidis* was very unexpected since there are major differences between *S. aureus* and *S. epidermidis,* in terms of bacterial type, structure, and the different nature of the proteins and polysaccharides expressed therein, and thus it was not at all expected that an antibody recognizing CNA19 of *S. aureus* would recognize epitopes from *S. epidermidis* as well. In particular, it is in fact the case that *S. aureus* are coagulase-positive staphylococcal bacteria, and *S. epidermidis* are coagulase-negative staphylococcal bacteria. Further, many proteins and polysaccharides expressed in *S. aureus* are not expressed in *S. epidermidis*, and vice versa.

3. Further, the ability of the monoclonal antibody to CNA19 to actually displace collagen from the extracellular matrix protein and in effect detach *S. aureus* cells adhering to collagen was one of the most remarkable and unexpected properties observed in the study of this antibody. Previously, no such displacing behavior had been observed, and it had not previously known or expected that any particular antibodies to extracellular matrix proteins (or MSCRAMM®s) could actually act to displace bacteria that was already adhering to the collagen or other MSCRAMM®s on the cells. Indeed, not only was this displacing behavior shown in our experiments (such as disclosed, e.g., in Example 2 of the specification), it was also the case that bacteria that had adhered to a collagen substrate for up to at least 5 hours could still be displaced by the monoclonal antibodies to CNA19 in accordance with the present invention. This unexpected beneficial property will make the monoclonal antibodies of the present invention particularly effective in cases wherein a prior infection is present.

4. In this regard, in contrast to the Examiner's claim that our prior patents and applications relating to the full CNA protein (such as U.S. Pat. No. 6,288,214) disclosed antibodies "capable of displacing S. aureus to collagen", this property was not shown in those references, and indeed, none of our prior references disclosed or suggested the particular monoclonal antibody of the present invention, namely a monoclonal antibody to CNA19 (a region of amino acids 151-318 of the CNA protein) which is cross-reactive with *S. epidermidis*. Similarly, our previous antibodies to the full CNA protein were not shown to be cross-reactive with *S. epidermidis*, and thus the Examiner's position that these particular CNA antibodies were cross-reactive is not correct.

5.. Even further, I have reviewed the Examiner's comments that the prior antibodies to the full CNA protein and to the M55 region (SEQ ID NO:6 of U.S. Pat. No. 6,288,214) would necessarily also recognize the CNA19 region at amino acids 151-318 of the CNA protein, and such comments are untrue, particularly in the case of monoclonal antibodies. Indeed, monoclonal antibodies are based on a very specific epitope within a given region, and thus it is extremely unlikely that a monoclonal antibody raised against a far greater region would be able to recognize the specific epitope or epitope of the monoclonal antibody to the specific region. Accordingly, it is clearly **not** the case that the prior antibodies to the full CNA protein or to the M55 region (amino acids 30-531) would specifically recognize the CNA19 region, and our prior

references did not disclose or suggest the present monoclonal antibody to CNA19 which has the unexpected beneficial features as set forth above.

6. In addition to the above information, it is also the case that no one can produce a monoclonal antibody to any particular region or epitope with any reasonable certainty that such a monoclonal antibody will be successful in achieving protection against infection. Accordingly, the fact that the present monoclonal antibody to CNA19 has the beneficial properties recited above, including displacing activity and cross-reactivity, is totally unexpected since it has been very hard to predict with any certainty which monoclonal antibodies to which proteins, or fragments or domains, will result in antibodies capable of afforded protection against infection.

7. A perfect example of the uncertainty in this field is shown in the attached Abstract from the article Ichiman et al., Can J Microbiol. 1991 May; 37(5):404-7, attached hereto as Exhibit 1. In that article, the authors disclose the fact that passive protective activities of three different classes of monoclonal antibodies in mice against challenge with strain ATCC 31432 (capsular type I) of Staphylococcus epidermidis were examined, and that while the monoclonal IgM antibody did passively protected mice against challenge with the homologous strain, "monoclonal IgG1 and IgG2b antibodies did not." It is thus very uncertain as to which monoclonal antibodies will function at all to provide adequate protection against infection. It is also uncertain with any given region within a target protein which monoclonal antibody against which target region will be successful in protecting against bacterial challenge.

8. Accordingly, before one actually goes forward with attempting to prepare a monoclonal antibody based on any particular surface protein, there are no guarantees that such an antibody can be adequately produced, much less with any certainty that the resulting monoclonal antibody will have success in achieving protection against infection. It is also uncertain as to which particular epitope of any particular protein will result in a protective monoclonal antibody. It was thus an unexpected result that monoclonal antibodies raised against the CNA19 by my inventive group provided the properties as set forth above and gave excellent results in achieving protection well beyond that which would have been expected by one of ordinary skill in the art.

9. Finally, I have reviewed the Examiner's rejections on the basis of the Schiotz and Espersen references, and it is clear that these references have nothing whatsoever to do with the present invention and do not disclose or suggest any antibody to CNA or one of its binding regions, much less the specific CNA19 region in accordance with the present invention. In the rejection, the Examiner stated that the Schiotz reference disclosed a cross-reactive antibody that "was generated against sonicated antigens from S. aureus that includes CNA-19 region." See the Official Action at page 11, last paragraph. Similarly, with regard to Espersen, the Examiner stated that this reference disclosed an antibody which "recognizes antigens of all S. aureus strains that includes CNA19 region." See the Official Action at page 12, middle paragraph. It is obvious that the Examiner is assuming that the CNA protein is somehow inherent in each and every S. aureus strain and for that reason alone she concludes it must be

present in the strains utilized in these references. Not only is the Examiner's position untrue, the opposite is the case and there are in fact many strains of S. aureus which **do not even possess the CNA gene and protein.** This is shown for example in the enclosed Abstract (attached as Exhibit 2) from Smeltzer et al., Poult. Sci. 79(7):1042-9 (July 2000) which states that "To date, only one collagen-binding adhesin (Cna) has been identified, **and the gene encoding this adhesin (cna) is not present in most S. aureus strains.**" (Emphasis added).

10. In short, neither Schiotz nor Espersen disclose, inherently or otherwise, any CNA binding proteins nor antibodies thereto, much less the specific monoclonal antibody directed to CNA19 in accordance with the present invention.

I hereby state that all statements made herein based on my own personal knowledge are true and correct and that all statements based on my information and belief are true and correct to the best of my knowledge, and further that all of these statements have been made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

5-5-05
Date

Joseph M Patti
Dr. Joseph M. Patti, Ph.D.

Can J Microbiol. 1991 May;37(5):404-7.

Monoclonal IgM antibody protection in mice against infection with an encapsulated strain of Staphylococcus epidermidis.

Ichiman Y, Usui Y, Suganuma M, Yoshida K.

Department of Microbiology, St. Marianna University School of Medicine, Kawasaki, Japan.

Passive protective activities of three different classes of monoclonal antibodies in mice against challenge with strain ATCC 31432 (capsular type I) of Staphylococcus epidermidis were examined. Monoclonal IgM antibody passively protected mice against challenge with the homologous strain, whereas monoclonal IgG1 and IgG2b antibodies did not. The protective activity of IgM was absorbed by the cell surface antigen extracted from the homologous strain but not by the antigen from heterologous strains. Rapid reduction of viable cells took place in the peritoneal cavity of mice immunized with monoclonal IgM as early as 6 h after the challenge with the homologous strain. An enzyme-linked immunosorbent inhibition assay showed there was remarkable inhibition with the homologous cell surface antigen but not with heterologous preparations from other strains. Results suggest that in the mouse the major passive protection against the S. epidermidis strain is provided by the IgM antibody to the cell surface antigen.

EXHIBIT 1

: Poult Sci. 2000 Jul;79(7):1042-9.

Molecular pathogenesis of staphylcoccal osteomyelitis.

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Staphylococcus aureus is the most prominent musculoskeletal pathogen of man and animals. The persistent emergence of antibiotic-resistant strains has prompted renewed efforts to develop alternative protocols for the treatment and prevention of staphylococcal disease. These efforts have included attempts to develop an effective staphylococcal vaccine. Among the potential vaccine candidates are a group of surface proteins that act as adhesins by virtue of their ability to bind host proteins present in plasma and in the extracellular matrix. Because of our interest in the treatment and prevention of musculoskeletal infection, we have focused on adhesins that contribute to the colonization of bone and cartilage. Based on reports suggesting that colonization is a conserved characteristic of S. aureus strains that cause osteomyelitis and septic arthritis, we have paid particular attention to the factors that contribute to the ability to bind collagen. To date, only one collagen-binding adhesin (Cna) has been identified, and the gene encoding this adhesin (cna) is not present in most S. aureus strains. The possibility that a rare phenotype is conserved among isolates that cause a particular form of infection suggests a cause-and-effect relationship in which the phenotype contributes to the pathogenesis of the disease. To further evaluate that hypothesis, we attempted to determine whether Cna is the only collagen-binding adhesin produced by S. aureus and whether strains that encode cna share additional characteristics that distinguish them from other S. aureus strains. We also studied whether immunization with Cna induces a protective immune response. Our results confirm that Cna is the primary and probably the only collagen-binding adhesin and that the genetic element encoding cna does not encode any additional virulence factors. These results strongly suggest that the only consistent difference between cna-positive and cna-negative strains is the ability to bind collagen. We also demonstrated that vaccination with a recombinant fragment of Cna can protect animals against septic death and limit the ability to colonize bone.

EXHIBIT 2